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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,168	12/04/2001	Thomas J. Brennan	R-10	6874

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,168	BRENNAN, THOMAS J.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-37 is/are pending in the application.

4a) Of the above claim(s) 1,2,13 and 35-37 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 3-12 and 14-34 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

New Fig. 3 has been entered. The amendment to the description of Fig. 3 has been entered.

Election/Restrictions

Applicant's election without traverse of Group II (claims 3-12, 14-34) in the paper filed 7-20-03 is acknowledged.

Claims 1, 2, 13 and 35-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. The requirement is made FINAL.

Claims 3-12 and 14-34 are under consideration in the instant office action.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 3-12 and 14-34 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility.

Claims 6, 7 and 14-33 are directed toward a transgenic animal having a disruption of an A2D2 calcium channel subunit gene. Claims 10 and 34 are directed toward methods of using the mice to identify compounds. The specification teaches making A2D2 -/- mice. The specification lists numerous tests to run on the mice to

determine their phenotype (pg 21-27). The mice had perinatal lethality and abnormal behavior, posture, body shape, eyes, growth and immune system. Heterozygous mice were not tested (pg 53, lines 7-24; pg 54 and 55, Tables 1-3). The specification suggests using the mice as a model of genetic disease but does not disclose a specific disease in humans linked to a disruption in A2D2 (pg 18, pg 20, lines 8-12).

The art at the time of filing taught "ducky mouse" had a disruption in A2D2 and a phenotype of "ataxic, wide-based gait and paroxysmal dyskinesia, small size and a failure to breed or survive beyond 35 days;" the art did not teach how to use such a mouse as a model of disease (Barclay, Aug. 15, 2001, J. Neurosci., Vol. 21, No. 16. pg 6095-6104; pg 6095, col. 2, 2nd ¶). Since the time of filing, Brodbeck (March 8, 2002, J. Biol. Chem., Vol. 277. No. 10, pg 7684-7693) taught mice having a disruption of the A2D2 gene are a model for "absence epilepsy," which is not taught or suggested in the instant application.

The mouse claimed does not have a specific utility. The specification does not teach a disruption in A2D2 correlates to any specific disease in humans. For example, A2D2 has not been linked to dwarfism (claim 22) in humans. While claims 14-33 are directed toward mice having particular characteristics, the characteristics are not specific to any disease. For example, abnormal gait (claim 19) is not specific to any disease. Using the mice claimed to identify compounds is not specific to the mouse claimed because wild-type mice may be used to identify such compounds. Therefore, using the mouse claimed to identify compounds is not specific to that mouse, and the mouse claimed does not have a use that is specific to any disease in humans.

The mouse claimed does not have a substantial utility. The mice die shortly after birth (perinatally); the specification does not teach how to use a mouse that dies perinatally (claim 20). Such mice are not useful in testing compounds because a phenotype in the mouse would have to be observed over a significant period of time. The specification does not teach how to use a mouse that has abnormal organ weight (claims 24-27), posture (claim 29-30), small eyes (claim 32) or squinting eyes (claim 33). Claims 10-11, step c) require administering compounds to the mice and determining whether A2D2 gene expression is modulated. Compounds that modulate A2D2 expression cannot be found using the mice because A2D2 is not expressed in the mice. Claim 34 requires administering compounds to the mice and determining whether a particular phenotype is ameliorated. The specification states the mouse may be used to test compounds relating to behavioral phenotypes (pg 20, line 8-12). Compounds that modulate behavioral phenotypes in the mice described in the specification are not useful because no behavioral phenotypes are linked with A2D2 in humans. No human genetic diseases, such as neurological, neuropsychological or psychotic illnesses (pg 20, line 12), are linked to the A2D2 gene. The specification does not identify any compounds that alter behavioral phenotypes using the mice. Therefore, using the mouse to identify compounds is not substantial.

Claim 9 is included because it is directed toward making the mouse, which lacks utility for reasons above. Claims 3-5, 8 and 15, directed toward cells having a disrupted A2D2 gene, and claims 11-12, directed toward using the cells to test compounds, are included because the cells lack a specific and substantial utility for the reasons above.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-12 and 14-34 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition, the specification does not reasonably provide enablement for any animal, A2D2 gene, phenotype, cell, disruption, method of making a transgenic or method of using a transgenic as broadly claimed.

Claims 6, 7 and 14-33 are directed toward a transgenic animal having a disruption of an A2D2 calcium channel subunit gene. Claims 10 and 34 are directed toward methods of using the mice to identify compounds. The specification teaches making A2D2 -/- mice. The specification lists numerous tests to run on the mice to determine their phenotype (pg 21-27). The mice had perinatal lethality and abnormal behavior, posture, body shape, eyes, growth and immune system. Heterozygous mice were not tested (pg 53, lines 7-24; pg 54 and 55, Tables 1-3). The specification suggests using the mice as a model of genetic disease but does not disclose a specific disease in humans linked to a disruption in A2D2 (pg 18, pg 20, lines 8-12).

The specification does not enable making or using a transgenic with a wild-type phenotype as encompassed by the claims. The transgenics throughout many of the claims do not recite any phenotype and may, therefore, have any phenotype including wild-type phenotype. The specification does not provide any use for a transgenic having a disruption in A2D2 that has a wild-type phenotype. The only disclosed phenotype for the transgenic claimed is one that correlates to a mutation in A2D2. Therefore, the claims should recite a non-wild-type phenotype that correlates to a disruption in A2D2.

The specification does not teach how to make animals or cells having a disruption in an A2D2 gene other than mice (claims 3-8). Specifically, claims 4-5 encompass mice and rat cells. "Murine" encompasses mice and rats (http://www.m-w.com/cgi-bin/dictionary?book=Dictionary&va=murine). The only means of making a cell with a disruption in A2D2 taught in the specification is by using mouse embryonic stem cell technology. The state of the art at the time of filing was such that embryonic stem (ES) cell technology had only been successful in mice. Wagner (May 1995, Clin. and Experimental Hypertension, Vol. 17, pages 593-605) and Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) taught germline transmission of ES cells has not been demonstrated in species other than mice and the growth of ES cells from species other than mice is unreliable. Wall (1996, Theriogenology, Vol. 45, pg 57-68) taught transgene expression and the physiological result of such expression in livestock was not always accurately predicted in transgenic mice (page 62, line 7). The specification fails to provide sufficient guidance to make transgenics other than mice by teaching

obtaining ES cells in species other than mice. The specification does not teach the nucleic acid sequence of the A2D2 gene in non-mice, non-human species or correlate the A2D2 gene in mice to the A2D2 gene in other species. The specification does not teach how to make knockout animals other than mice or correlate making knockout mice to other species. Therefore, the specification does not provide adequate guidance for one of skill in the art to make a transgenic, non-human animal or cells having a disruption in A2D2 in any species other than mice.

The specification does not provide adequate correlation between the phenotype obtained in mice to the phenotype obtained in other species. The state of the art at the time of filing was that the phenotype of transgenic mice does not predict the phenotype in non-mice species. Models of human diseases have relied on transgenic rats when the development of transgenic mice having the desired phenotype was not feasible. Mullins (1990, Nature, Vol. 344, pg 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse Ren-2 renin transgene. Hammer (1990, Cell, Vol. 63, pg 1099-1112) describes spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human b_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins, 1989, EMBO, Vol. 8, pg 4065-4072; Taurog, 1988, J. Immunol., Vol. 141, pg 4020-4023) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. Therefore, the specification does not enable making transgenic having the disclosed phenotypes in species other than mice.

Claim 9 is directed toward a method of making a transgenic mouse having a disruption in A2D2 using a cell having a construct with two sequences of A2D2, introducing the cell into a blastocyst, implanting the blastocyst into a pseudopregnant mouse which gives birth to chimeric mice, and breeding the chimeric mouse to produce the transgenic mouse. The claim does not require using mouse cells or an embryonic stem cell, which is considered essential to the invention. A mouse ES cell is the only type of cell taught in the specification that can be introduced into a blastocyst and result in a chimeric mouse as claimed. The claim does not require the mouse have a non-wild type phenotype, which is required for reasons cited above. Given the unpredictability in the art taken with the guidance provided in the specification, the cell in a) should be a mouse ES cell, the blastocyst in b) should be a mouse blastocyst, and the transgenic mouse produced should have a genome comprising a homozygous disruption in A2D2, wherein said mouse lacks functional A2D2 and has a disclosed phenotype.

Claims 10-12 and 34 are directed toward methods of screening compounds using a cell or mouse having a disruption in an A2D2 gene. Step (c) requires determining whether the expression or function of A2D2 is modulated but the mice and cells do not express A2D2. The specification does not teach how to determine A2D2 expression in mice having a disruption in A2D2. While the specification teaches transgenics having particular characteristics, the specification does not teach how to use mice

having such characteristics in an assay to determine whether a compound modulates A2D2; the compound may modulate some other protein. Without such a disclosure, the specification does not provide adequate guidance for one of skill to use the mouse disclosed to determine compounds that modulate A2D2 expression or function.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 and 14-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The metes and bounds of what applicants consider "significant" expression cannot be determined making claim 14 unclear.

The metes and bounds of what applicants consider "abnormal" cannot be determined because the term has various meanings to those of skill in the art and because the term is not defined in the specification. Therefore, claims 16-34 are indefinite.

The term "derived" in claims 12 and 15 is indefinite. It cannot be determined if the claim is limited to cells having a disruption in A2D2 isolated from the transgenics or if the claim encompasses cells isolated from the mouse then made to have the disruption.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3, 4, 6-8 and 14-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Snell (1955, J. Hered. Vol. 46, pg 27-29) as supported by Barclay (1998, J. Clin. Invest., Vol. 101, pg 689-695).

Snell taught the ducky mouse mutant. Barclay taught the ducky mouse mutant had a disruption in an A2D2 gene and had an "ataxic, wide-based gait and paroxysmal dyskinesia, small size and a failure to breed or survive beyond 35 days" (pg 6095, col. 2, 2nd ¶).

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER